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Six months neoadjuvant imatinib improves resectability potential of gastric stromal tumors in Egyptian patients

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ABSTRACT

Objectives: Though recurrence is high, local excision is the preferred approach for dealing with gastric stromal tumors. Achieving negative margins is mandatory, sometimes requiring subtotal gastrectomy. Adjuvant imatinib is essential for advanced cases and prolonging survival; however, there is not enough data to recommend its use before surgery to increase resectability. The current study aims at investigating this concept in Egyptian patients.

Patients and methods: The study included 16 patients (13 males, 3 females, mean age 60 years) presenting with gastrointestinal stromal tumors (GISTs) who were candidates for emergency ($n = 3$) or elective ($n = 13$) surgery. Investigations included endoscopy (+biopsy), sonography, and computed tomography (CT). Patients were enrolled in two groups: A ($n = 6$: projected to planned surgery) and B ($n = 7$: harboring c-kit +ve tumors). Each B patient received imatinib (400 mg/day) for 6 months before surgery. Clinical and radiological evaluation was at day 100. The Chi-square test was used to check size changes, and p at <0.02535 was considered significant.

Results: All patients had abdominal discomfort, while 62.5% had epigastric pain, and 12.5% had hematemesis. Tumor sizes ranged from 8.4 to 20 cm 2/3 were located in the upper stomach. Five patients (31.3%) harbored lesions with low risk malignancy, eight (50%) with moderate risk and three (18.8%) with high risk. Wedge gastrectomy was the most common operation performed (81.25%) while partial gastrectomy was carried out in the rest, reporting no recurrence for 6 months. Not determined in group A patients, c-kit status was strongly positive in all members of group B; in two of them treatment was suspended due to poor response.

Conclusion: Imatinib has an acceptable safety profile and can be considered as a neoadjuvant therapy in GISTs. Until clear guidelines have been developed, we report that a 6 month intake may noticeably increase their resectability potential and improve prognosis.

1. Introduction

Gastrointestinal stromal tumors (GISTs) were not recognized as a distinct entity until their origin from the interstitial cells of Cajal – or their predecessors – was established. These turn into epithelioid, undifferentiated cells branded by over expression of the tyrosine kinase receptor KIT (CD117)[1,2] GISTs span a wide clinical spectrum from benign to highly malignant or even metastatic,[3] and harbor the potential risk of local and distant recurrence making them difficult to cure.[4,5] The only treatment for metastatic disease is surgery, while chemotherapy and radiation treatments have proven ineffective.[4] While the minority of GISTs affect the small intestine, colon, rectum and mesentery, studies also demonstrate their prevalence in the stomach (60%), particularly in elderly males, reaching a zenith at age 60 years,[6–8] though occasionally also affecting children. Requiring immediate surgery, bleeding is the most common presentation of gastric stromal tumors (50%) and is usually associated with ulceration in the lumen.[9] Other patients present with abdominal pain, palpable mass, obstructive symptoms or minor bleeding episodes.[6] Endoscopy can possibly disclose the gastric tumor as a submucosal mass, and computed tomography (CT) [or magnetic resonance imaging (MRI)] scans may give diagnostic suggestions, but a firm diagnosis is only certain after pathologic study of the biopsy or resected specimens. Being sensitive, rapid and reliable,[10] it is preferable to keep CT scans to measure response to adjuvant therapy if used after surgery. It is difficult for surgeons to select the most suitable procedure to pursue, and as late as 2001 local resection was considered adequate.[11] The rapid

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Table 1
Group B ($n = 7$) Reason for giving neoadjuvant imatinib followed by delayed surgery.

Sn	Reason	Notes
1	Vague but strongly symptomatic local recurrence after previous wedge resection.	[a] [b]
2	Noncomplicated large antral lesion (>12 cm).	[b]
3	Radiologically resectable lesion but with solitary left lobe secondary.	[b]
4	Greater curvature mass very close to the splenic hilum and pancreatic tail. Resection without splenectomy was thought impossible.	[b]
5	Localized large sized mass recurrent after previous wedge gastrectomy (distal stomach) with extragastric lymph node metastasis.	[a]
6	Large tumor at greater curvature very close to body of pancreas and acquiring accessory blood supply from there.	[b]
7	Greater curvature large mass. Heavy adhesion to the greater omentum in CT.	[b]

[a] Patient did not receive imatinib following previous surgery.
[b] Considered temporarily irresectable due to local reasons. Large size is the cause in cases 2, 5 and 6.

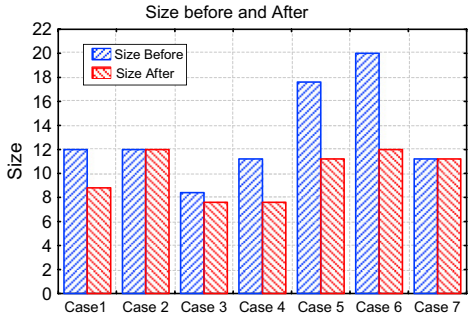
recurrence that follows was attributed to removing the inhibition exerted by the primary tumor on its remote metastases via circulating angiostatin.[12,13] Currently, achieving negative surgical margins on frozen section examination is mandatory[14] and this entails segmental resection, at times amounting to subtotal gastrectomy and omentectomy as in perforation, bleeding or when a tumor ruptures.[9,15] Being of no profitable use lymphadenectomy is not required and adjuvant therapy with the KIT tyrosine kinase inhibitor imatinib remains essential for high risk or metastasizing tumors, as it significantly prolongs survival.[16,17] Recently, much attention has been focused on using this drug as a neoadjuvant therapy,[18] but earlier reports included diminutive formal analyses of data concerning success rates that might have been caused by this approach. Notwithstanding this, and being impressed by the amazing pathological response it induces, particularly on tumor volume,[19] the need to launch this new discipline on Egyptian patients was recognized.

2. Patients and methods

This prospective study was completed at Cairo University hospitals and also in private practice, from May 2007 through to January 2009. It included 16 patients (13 males, 3 females, ages ranging from 38 to 72 years (mean = 60)) presenting with suspected gastric stromal tumors and who were candidates for emergency ($n = 3$) or elective ($n = 13$) surgery. Investigations included endoscopy, endosonography and endoscopic biopsy, while extra luminal spread and lymph node status were assessed by CT; however, one patient required percutaneous drainage of abdominal sepsis as a preliminary step. Meticulous analyses of patients' symptoms were enough in all cases to suggest that GIST was likely and investigations were needed only to confirm diagnosis and to assess operability. In six of those patients, tumors were immediately amenable to planned surgical resection and were sequestrated as group A, while the remaining seven patients – all harboring tumors with c-kit +ve biopsy specimens – were enrolled as group B. Though all lesions in group B patients were localized in CT, it was unwise from the surgeon's perspective to proceed immediately due to different reasons (Table 1). To improve compliance, it was important to clarify to each individual patient what GIST is, and to assure him that his illness may be controllable, and to provide him with full information about the treatment protocol, and to have his signed consent. Each group B patient received imatinib (400 mg/day orally) for 6 months before surgery. Clinical and radiological evaluation of drug effect was at day 100, and the Chi-square test was used to check the significance of size reduction induced by treatment. A value of $p < 0.02535$ was considered significant. Two patients had a poor response to the drug and were shifted to classical management as in group A. Imatinib–associated side effects were not identified in this series.

3. Results

Clinically, all patients presented with abdominal discomfort, while only 10 of them (62.5%%) had epigastric pain, and two (12.5%) had hematemesis. Mean tumor size was 13.2 cm (8.4–20), mostly located in the upper stomach (68.8%). Five patients (31.3%) harbored lesions with low risk malignancy, eight with moderate (50%) and three (18.8%) with high risk. While strongly positive in the seven patients who received neoadjuvant imatinib, the c-kit status was not determined in patients of group A. Preoperative imatinib for 6 months succeeded in inducing spectacular symptomatic improvement in five patients with an overall reduction in tumor size of 29%, as seen via CT (Fig. 1), with a concomitant reduction in tumor density, which subsequently made resection



Friedman ANOVA and Kendall Coeff. Of Concordance
ANOVA Chi Sqr. (N = 7, df = 1) = 5.000000 p < .02535
Coeff. Of Concordance = .71429 Aver. Rank r = .66667

	Average	Sum of	Mean	Std.Dev.
Size Before	1.857143	13.00000	13.20000	4.072673
Size After	1.142857	8.00000	10.05714	1.992366

Observed vs. Expected Frequencies
Chi-Square = 7.613939 df = 6 p < .267776
NOTE: Unequal sums of obs. & exp. frequencies

	Size After	Size Before	A - B	(A-B)**2
Sum	70.40000	92.40000	-22.0000	7.613939

Fig. 1. Analysis of statistical data.

Table 2
Group B (n=7) Patient/tumor characteristics and management and results.

SN[a]	Age (years)	Location[f] & size (cm)	Indication for neo-imatinib	Residual size (RS) in cm	(RS) % of initial[e]	Response rate	Postoperative histpathology	Post-ttt op.procedure
1	61	D/12	Unresectable[b]	8.8	73.30	26.7	Hypocellularity + necrosis	WG
2	55	P/12	Unresectable	12[d]	–	–	–	
3	59	P/8.4	Unresectable	7.6	90.5	9.5[c]	Hypocellularity + necrosis+cysts	WG
4	63	P/11.2	Unresectable	7.6	67.90	32.1	Hypocellularity + necrosis	WG
5	58	P/17.6	Large size	11.2	64.20	35.8	Hypocellularity + necrosis	PG
6	60	P/20	Large size	12.0	60.00	40.0	Necrosis	PG
7	48	P/11.2	Unresectable	11.2[d]	–	–	–	

[a] All are males with histologically proven c-kit + ve gastric stromal tumors.
[b] Unresectability determined preoperatively by CT or MRI.
[c] Poor response.
[d] No response – treatment suspended.
[e] Average residual size % of the initial = 71.18%.
[f] Location in stomach in D : distal – P: proximal (%) Reduction in size = Mean Response rate: 28.82% Type of gastrectomy: WG: Wedge PG: Partial.

unexpectedly easy and trouble-free and also allowed for a lesser resection. Having no operative mortality, wedge gastrectomy was the most common procedure (81.25%) while partial gastrectomy was performed in three patients (Table 2). Within the following 6 months there was no evidence of recurrence. In two patients the response to the drug was poor and treatment was suspended.

4. Discussion

Currently, most clinicians working on GISTs recommend attempting complete or near complete surgical resection of gastric lesions. Low grade tumors have excellent prognosis and resection may be curative, while recurrence is the rule in high grade ones. For the latter, post operative imatinib is suggested even if resection is incomplete,[17] as this is associated with a survival benefit when compared to imatinib[18] or surgery alone. This must be followed by strict follow-up even if the response is outstanding, repeating surgery if recurrence occurs. Only a little is known about using this drug prior to surgery[19,20] and the aim of this present trial was to study this modality in Egyptian patients. In our minds it was clear that gastric lesions, in particular, reveal themselves by their large sizes and that resection may be difficult or incomplete, particularly when extragastric lymph node metastasis is present and/or the tumor is fixed to adjacent organs, as in case numbers 4, 6 and 7 of the present series. This creates an ideal situation for making use of preoperative imatinib to increase resectability potential. Likewise, a comprehensible study performed by Florien in 2007 demonstrated appreciable reduction of tumor diameter in a linear fashion following preoperative imatinib therapy, monitoring at the same time a concomitant exponential reduction in volume; the latter being more sensitive for disclosing tumor response than diameter measurement.[21–23] Hohenberger et al. recently reported 18 patients manipulated in this way and concluded that even a partial response reflects a better outcome than in progressive disease.[24] In the present study, the efficacy of imatinib on the tumor size was adequately disclosed on CT, showing a 29% reduction -with or without cystic changes- and histological examination detected residual (or no) tumor cells, scant vascularity and scattered inflammatory cells. Reduction in tumor size was accompanied by reduction in tumor density observed in the preoperative CT and the local causes in cases 4, 6 and 7 were less evident. These results are strikingly similar to the results reported by Andtbacka et al.[25] 2 years ago who also advised performing surgery as early as possible after imatinib therapy as complete resection is rarely achieved once tumor progression re-occurs. The c-kit immunohistochemistry in tumor cells in the seven patients receiving pre-treatment was strongly positive (four were highly malignant), while in two patients poor response dictated treatment suspension. In no case was the remission complete; the same was also observed by Langer et al. in 2003.[26] Due to this achievement, we advocate regularly following the neoadjuvant policy in dealing with GISTs, but a universal decision to switch to this new regimen needs further studies. In fact, we share Raut[27] and his viewpoint that it is too early to do so now, and even to adequately determine the dose of the drug, optimal duration of treatment and to select the best time of surgical intervention. We propose the latter to be immediately after maximal drug effect but before possible disease progression caused by secondary mutations.[28] However, until more dose-response studies become available, surgeons who want to adopt this regimen should use the lowest effective dose for the shortest possible duration; 400 mg daily for 6 months is most likely the optimum. Escalation or doubling the dose has no effect as tolerance is not known. Should no evidence of response appear clinically or in the CT in the first month, then treatment must be stopped, and resection arranged for. Moreover, it is reasonable to notify patients receiving the drug about probable side effects and one should be aware about the disadvantage of using the drug in type 2 diabetics receiving insulin,[29] and also in patients with splenomegaly.[30] The real concern with this regimen is the possibility of developing resistance to imatinib which is ascribed to secondary mutations, as happens in myeloid leukemia; this is an expected concern in metastasizing cases intended to receive post operative therapy. Testing for this mutation in resected material[31,32] is a missing item from this work.

5. Conclusion

In the wake of the recent thesis on this neoadjuvant approach for malignancy, it might be relevant to start thinking of making use of such a function as the imatinib treatment of gastric stromal tumors. Our findings at this juncture are encouraging despite the small number of patients, absence of a control group and also in the face of observably deficient earlier clinical trials. Until clear guidelines are developed, a daily dose of 400 mg before surgery may be valid for increasing resectability potential. A 6 month treatment succeeded in reducing tumor size by 29%, but individual dose titration is not recommended. Also, an absent early response means prompt switching to surgery.

Conflict of interest
This is a single center study. There is no conflict of interest with other people or organizations.

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Ethical approval
Council General Surgery – Cairo University/Cairo, Egypt.

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